IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/786,907
Filing Date:	February 25, 2004
Applicant:	Bjarne Bogen
Group Art Unit:	1643
Examiner:	Lynn Anne Bristol
Title:	MODIFIED ANTIBODY
Attorney Docket:	36731S-000001/US

Commissioner for Patents
P.O. Box 1450
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Sir:

DECLARATION UNDER 37 C.F.R. §1.132

I, E. Sally Ward Ober, Ph.D., hereby declare as follows:

1. I am a professor in the Department of Immunology at the University of Texas Southwestern Medical Center in Dallas, Texas, USA.

2. I hold a Ph.D. in Biochemistry/Molecular Biology from the University of Cambridge, England.

3. I have read the following documents:

   (a) U.S. Patent Application Serial No. 10/786,907, filed on February 25, 2004.

   (b) Office Action dated June 1, 2010 for the above application.

(c) Herman U.S. Pub. No. 2005/0069549 (hereinafter "*Herman*").

(d) Slavin-Chiorini et al. Int. J. Can. 53:97-103 (1993) (hereinafter "*Slavin-Chiorini*").

3. I understand that prosecution of the present application may be advanced by presentation of evidence that there is no apparent reason for a person of ordinary skill in the art to combine and modify *Herman* in view of *Slavin-Chiorini*.

4. It is my position that a person of ordinary skill in the art would not combine and modify the *Herman* document in view of the *Slavin-Chiorini* document because *Herman* refers to prolonged serum half-life as desirable, and consequently a skilled artisan would not turn to *Slavin-Chiorini* in order to modify the *Herman* disclosure to decrease the half-life of the multispecific ligand.

5. In support of my position, please consider the following:

(a) *Herman* deals with immunotherapy where a prolonged serum half-life is desirable.

(b) *Herman* specifically discloses that it is desirable to increase the half-life of the multispecific ligand, as evidenced by the following paragraphs:

> [0069]: "…(which Fc if it includes the CH3 is preferably mutated to preclude its binding and/or increase its half life as is known in the art see U.S. Pat. No. 6,121,022)…"
>
> [0104]: (last sentence) "…Methods of prolonging the half-life of antibodies, producing bispecifics, scfvs and dsFvs and altering Fc effector function are well known and noteworthy references include U.S. Pat. No. 6,277,375, U.S. Pat. No. 5,869,046…"
>
> [0167]: "…The invention contemplates a variety of different size multifunctional ligands (MRU, single domain, scFv, Fab, minibodies, $F(ab)_2$, $F(ab')_2$, substantially whole antibodies etc. and known or obvious multimers thereof referenced herein and in the referenced literature) that are most suitable (eg. for small enough or, for example, having longest half life in circulation) for particular modes of administration to the extent that this is a limitation (eg. size, where drainage into the lymphatic system is sought to be increased or optimized)…"
>
> [0338]: "…For example, the carbohydrate moiety can be used to attach polyethylene glycol in order to extend the half-life of an intact antibody, or

antigen-binding fragment thereof, in blood, lymph, or other extracellular fluids…"

[0428]: "…U.S. Pat. No. 5,055,289 Interferon antibody therapeutic compositions having an extended serum half-life…"

(c) Although *Herman* mentions the use of a minibody-CH3 (e.g., paras. 0069, 0116, 0167), this is distinct from the Vaccibody construct since minibody constructs (e.g., Hu et al., 1996, Cancer Res., 56, 3055-3061) contain two scFvs linked to two dimerized CH3 domains.

(d) The *Slavin-Chiorini* document relates to clinical diagnosis using modified monoclonal antibodies where there are undesired side-effects from the prolonged presence of radiolabeled antibodies or antibody fragments. In particular, a radiolabeled antibody can be pathogenic due to radiation exposure. Furthermore, the presence of a foreign antibody has the consequence that the antibody can act as an antigen and elicit a HAMA (Human Anti-Mouse Antibody) response. Accordingly, these side-effects are overcome in *Slavin-Chiorini* by lowering the plasma half-life of the antibodies by removing the CH2 domain.

(e) A HAMA response is only relevant if the antibody administered is murine and the antibody is administered to a human. As such, it is not clear whether the multispecific ligands taught in *Herman* can induce a HAMA response, since there appears to be no specific disclosure of a molecule that could do this. In *Slavin-Chiorini*, a HAMA is a real problem, because the antibody used is a murine monoclonal antibody which is immunogenic in humans. In the present invention, the induction of a HAMA response might be desirable since the overall goal is to use the Vaccibody to induce immunity.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1000 of Title 18 of the United States Code, and that such statements may jeopardize the validity of the application or any patent issuing thereon.

E. Q Ward Ober 10/25/10

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